PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/000034	05.01.2005	09.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07D403/06, A61K31/41

Applicant
RATIOPHARM GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Fanni, S

Telephone No. +49 89 2399 8712

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

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3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000034

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 43-44

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 43-44

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000034

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,9,41
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,9,41
Industrial applicability (IA)	Yes:	Claims	1,9
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III.

Claims 43-44 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). See also the paragraph on : "Industrial applicability" in item V below.

Any further reference in the present opinion to the novelty and inventive step of "the present subject matter" should be understood as referring to the searched subject matter.

Re Item IV.

The separate inventions/groups of inventions are:

Group 1: claims 1-4, 9-24, 35 (part), 36, 38-40, 41-44(part):

Claims related to the provision and use of Form A of rizatriptan benzoate.

Group 2: claims 5-8, 25-34, 35(part) 37, 41-44(part):

Claims related to the provision and use of From B of rizatriptan benzoate.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The present subject matter is directed towards crystalline forms of rizatriptan benzoate. For the purposes of unity of invention, Rule, 13.1 PCT stipulates that an international application must relate to one invention only or to a group of inventions so linked as to form a single general (inventive) concept. The only common feature between the group of inventions listed above is the compound known as rizatriptan benzoate (cf present page 1, second paragraph). However, after non-exhaustive, preliminary documentary search it appears that rizatriptan benzoate is known in the art from the disclosure of documents D1-D3 (*vide infra*). Thus, it cannot be considered as being a special technical feature within

the meaning of Rule 13.1 PCT, since being known, it makes no contribution to the art. Consequently there is lack of unity within the meaning of rule 13 PCT and the different inventions listed above, not belonging to a common inventive concept, have to be formulated as different subjects pursuant to Article 17(3) (a) PCT.

Re Item V

Reference is made to the following documents:

D1: EP-A-0 497 512
D2: US-A-5 567 824
D3: GB-A-2 315 67

Novelty (Article 33(2) PCT)

D1-D3 all show processes for the preparation of rizatriptan benzoate, sharing the same final step in which the crude rizatriptan benzoate is recrystallised from ethanol, a process which is encompassed e.g. by present claims 11 and 25. Thus, it appears that novelty over the prior art can only be established for both group of inventions 1 and group of inventions 2 as defined above, by providing data which clearly show that the distinguishing features (i.e. XRPD patterns) defining the present forms A and B of rizatriptan are not inherent features of the known form of rizatriptan, i.e. they are unambiguously attributable to the new crystalline forms claimed. In the absence of said data, novelty over D1-D3 cannot be acknowledged for the present subject matter.

Inventive step (Article 33(3) PCT)

For both group of inventions 1 and group of inventions 2, D1-D3 are all considered to be relevant prior art and disclosed method of synthesis and recrystallisation of rizatriptan benzoate.

The problem to be solved by the subject matter of both groups of inventions is considered the provision of a new polymorphic form of rizatriptan benzoate which have improved

characteristics (e.g. stability for extended periods of time) or exhibits improved pharmacokinetic properties (e.g. bioavailability) when compared with the known form of rizatriptan benzoate.

The solution of the said problem could be considered inventive only if it were shown that the distinguishing technical features of a given polymorphic form clearly differentiate these latter from those known from the prior art, and that the improved characteristics and/or properties can be unambiguously attributed to the crystalline structure of the said form. It appears therefore that an inventive step for both group of inventions 1 and group of invention 2 can be established only by means of comparative tests between the physical and/or pharmacokinetic properties of the present polymorphic forms A and B, and the crystalline form known from the prior art. In the absence of said comparative tests, an inventive step cannot be acknowledged for the present subject matter.

Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 43-44 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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Applicant
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2. **FURTHER ACTION**

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European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Fanni, S Telephone No. +49 89 2399 8712

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

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   c. time of filing/furnishing:

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3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000034

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 43-44

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 43-44

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

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☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

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Box No. IV Lack of unity of invention

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2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

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   see separate sheet

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Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,9,41
Inventive step (IS)	Yes:	Claims	
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Any further reference in the present opinion to the novelty and inventive step of "the present subject matter" should be understood as referring to the searched subject matter.

Re Item IV.

The separate inventions/groups of inventions are:

Group 1: claims 1-4, 9-24, 35 (part), 36, 38-40, 41-44(part):

Claims related to the provision and use of Form A of rizatriptan benzoate.

Group 2: claims 5-8, 25-34, 35(part) 37, 41-44(part):

Claims related to the provision and use of From B of rizatriptan benzoate.

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the meaning of Rule 13.1 PCT, since being known, it makes no contribution to the art. Consequently there is lack of unity within the meaning of rule 13 PCT and the different inventions listed above, not belonging to a common inventive concept, have to be formulated as different subjects pursuant to Article 17(3) (a) PCT.

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Novelty (Article 33(2) PCT)

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Industrial applicability (Article 33(4) PCT)

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

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International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000034

Box No. I Basis of the opinion

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because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

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☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
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the computer readable form	☐	has not been furnished
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☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

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   ☐ complied with

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Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,9,41
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,9,41
Industrial applicability (IA)	Yes:	Claims	1,9
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2. Citations and explanations

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Re Item III.

Claims 43-44 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). See also the paragraph on : "Industrial applicability" in item V below.

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The separate inventions/groups of inventions are:

Group 1: claims 1-4, 9-24, 35 (part), 36, 38-40, 41-44(part):

Claims related to the provision and use of Form A of rizatriptan benzoate.

Group 2: claims 5-8, 25-34, 35(part) 37, 41-44(part):

Claims related to the provision and use of From B of rizatriptan benzoate.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

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D3: GB-A-2 315 67

Novelty (Article 33(2) PCT)

D1-D3 all show processes for the preparation of rizatriptan benzoate, sharing the same final step in which the crude rizatriptan benzoate is recrystallised from ethanol, a process which is encompassed e.g. by present claims 11 and 25. Thus, it appears that novelty over the prior art can only be established for both group of inventions 1 and group of inventions 2 as defined above, by providing data which clearly show that the distinguishing features (i.e. XRPD patterns) defining the present forms A and B of rizatriptan are not inherent features of the known form of rizatriptan, i.e. they are unambiguously attributable to the new crystalline forms claimed. In the absence of said data, novelty over D1-D3 cannot be acknowledged for the present subject matter.

Inventive step (Article 33(3) PCT)

For both group of inventions 1 and group of inventions 2, D1-D3 are all considered to be relevant prior art and disclosed method of synthesis and recrystallisation of rizatriptan benzoate.

The problem to be solved by the subject matter of both groups of inventions is considered the provision of a new polymorphic form of rizatriptan benzoate which have improved

characteristics (e.g. stability for extended periods of time) or exhibits improved pharmacokinetic properties (e.g. bioavailability) when compared with the known form of rizatriptan benzoate.

The solution of the said problem could be considered inventive only if it were shown that the distinguishing technical features of a given polymorphic form clearly differentiate these latter from those known from the prior art, and that the improved characteristics and/or properties can be unambiguously attributed to the crystalline structure of the said form. It appears therefore that an inventive step for both group of inventions 1 and group of invention 2 can be established only by means of comparative tests between the physical and/or pharmacokinetic properties of the present polymorphic forms A and B, and the crystalline form known from the prior art. In the absence of said comparative tests, an inventive step cannot be acknowledged for the present subject matter.

Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 43-44 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.